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Docket No.: 05432/000J951-US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Connie Sánchez et al.

Confirmation No.: 7268

Application No.: 10/021,126

Art Unit: 1614

Filed: December 12, 2001

Examiner: F. Krass

For: Treatment of Neurotic Disorders

RESPONSE

MS Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed August 21, 2003, kindly consider the following remarks.

Claims 1-5, 10, 11, and 14 have been rejected under 35 U.S.C. §102(b) as anticipated by Lepola et al. (*J. Clin. Psychiatry*, 59:10, pp.528-534 (October 1998)). Lepola discloses the use of racemic citalopram to treat panic attacks. The Examiner contends that because the pending claims do not specify any optical purity and include the open-ended transitional phrase "comprising", they do not exclude the inclusion of the (-) isomer and, therefore, read on racemic citalopram.

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The pending claims are directed to a method of treating a neurotic disorder, such as panic attacks, by administering an effective amount of escitalopram.

A racemic mixture is a 1:1 mixture of (+) and (-) enantiomers. See the definition of "racemic" in Exhibit A. Therefore, racemic citalopram as disclosed in Lepola is a 1:1 mixture of the (+) or S-enantiomer of citalopram and the (-) or R-enantiomer of citalopram. In contrast, the term "escitalopram" refers to the S-enantiomer of citalopram. See the last paragraph on page 1 of the present application. In *In re May*, 574 F.2d 1082 (CCPA 1978), the predecessor court to the Court of Appeals for the Federal Circuit held that a claim reciting the levo enantiomer does not read on a racemate of the same compound. *Id.* at 1090 ("the novelty of an optical isomer is not negated by the prior art disclosure of its racemate"). A copy of the *In re May* decision is submitted herewith as Exhibit B. Similarly, escitalopram refers to the S-enantiomer of citalopram and does not encompass the racemate of citalopram. Therefore, claims 1-5, 10, 11, and 14 are not anticipated by Lepola. Accordingly, applicants respectfully request withdrawal of this rejection.

Claims 1-5, 10, 11, and 14 have been rejected under 35. U.S.C. §103(a) as obvious over Lepola in view of Boegesoe et al. (U.S.P. 4,943,950). Claims 12 and 13 have been rejected under 35. U.S.C. §103(a) as obvious over Lepola.

The Examiner contends that Boegesoe teaches that the activity of citalopram resides entirely in the (+) isomer (col.2, lines 38-40), and that it would, therefore, have been obvious to use the (+) isomer of citalopram, rather than racemic citalopram to treat panic attacks as disclosed by Lepola.

Submitted herewith as Exhibit C is an article entitled "R-Citalopram Attenuates Anixolytic Effects of Escitalopram in a Rat Ultrasonic Vocalisation Model" which was recently

published in the European Journal of Pharmacology by co-inventor Connie Sánchez (*Eur. J. Pharm.*, 464:155-158 (2003)). In the study reported in the article, co-inventor Sánchez surprisingly found that the R-enantiomer of citalopram ("R-citalopram"), when combined with escitalopram, inhibits the anti-anxiety (including anti-panic) activity of escitalopram.

The anxiolytic activity of escitalopram and R-citalopram was determined by footshock-induced ultrasonic vocalization in rats. Each group of rats was administered (i) a vehicle, (ii) escitalopram alone or in combination with R-citalopram, (iii) racemic citalopram, or (iv) R-citalopram alone. The rats were also tested at normal and enhanced levels of 5-hydroxytryptamine (5-HT).

The results for citalopram and escitalopram in normal rats and rats with enhanced levels of 5-HT are shown in Table 1 of the article, which is reproduced below.

Table 1

Administration (min before shock regimen)	Drug (30 min), s.c.		Drug (50 min) + 1-5HTP (25 mg/kg, 20 min), s.c.	
	ED_{50} (mg/kg)	Max inhibition (%)	ED_{50} (mg/kg)	Max inhibition (%)
Citalopram	ND[a]	64	1.1 0.69 - 1.8	100
Escitalopram	0.51 0.34 - 0.77	97	0.052 0.033 - 0.082	100

Results are expressed as ED_{50} values with 95% confidence intervals and % maximum inhibition

ND = not determined

a: biphasic response with maximum inhibition at 0.50 mg/kg

In normal rats, citalopram only partially inhibited ultrasonic vocalization (64% inhibition), while escitalopram nearly completely inhibited the response (97% inhibition). See the column entitled "Drug (30 min), s.c." in Table 1. When the basal levels of 5-HT in rats were increased by administering L-5-HTP (25 mg/kg), the median effective dose (ED_{50}) of citalopram was twice as much as that needed to obtain maximum inhibition in a normal rat. In contrast, the median effective dose of escitalopram in rats having enhanced levels of 5-HT was one-tenth ($^1/_{10}$) that needed to obtain maximum inhibition in a normal rat. In other words, escitalopram exhibits greater potency in rats with increased 5-HT levels than in rats at normal 5-HT levels, while citalopram exhibits decreased potency. Furthermore, escitalopram was about 20-times more potent than citalopram in the rats with enhanced 5-HT basal levels.

The ability of R-citalopram to attenuate (or reduce) the therapeutic effect of escitalopram was tested further by comparing the footshock-induced ultrasonic vocalisation in rats dosed with escitalopram alone and those dosed with escitalopram (0.24 mg/kg) and R-citalopram (0.48 mg/kg) concomitantly. Based on the test results shown in the insert of Figure 1 on page 156, Sánchez concluded that "[t]he addition of R-citalopram significantly attenuated the inhibitory effect of escitalopram on footshock-induced ultrasonic vocalization" (left column, last full paragraph, page 157).

These results demonstrate that R-citalopram attenuates the anxiolytic effect of escitalopram in footshock-induced ultrasonic vocalisation.

This is especially surprising because "it would be expected that R-citalopram's histamine H_1 receptor antagonistic activity would enhance rather than attenuate the effect of

escitalopram on foot-shock-induced ultrasonic vocalisation" (right column, last sentence of the second full paragraph, page 157).

> "Of the 144 targets tested in *in vitro* binding affinity studies ..., the only site for which citalopram and R-citalopram, but not escitalopram, showed appreciable affinity was that of the histamine H_1 receptor. *In vitro* studies in isolated guinea pig ileum show that R-citalopram is a weak histamine H_1 receptor antagonist (unpublished observation). Histamine H_1 receptors are involved in mediation of ultrasonic vocalization and the histamine H_1 receptor antagonist, mepyramine, antagonizes footshock-induced ultrasonic vocalization ... Thus, it would be expected that R-citalopram's histamine H_1 receptor antagonistic activity would enhance rather than attenuate the effect of escitalopram on footshock-induced ultrasonic vocalization." (italics added)

Therefore, the significantly greater potency of escitalopram compared to racemic citalopram for treating panic attacks is surprising and unexpected.

For the foregoing reasons, Lepola and Boegesoe alone or in combination fail to render obvious the presently claimed invention. Accordingly, applicants respectfully request withdrawal of this rejection.

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: November 21, 2003

Respectfully submitted,

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